PROMETRIUM - progesterone capsule
Solvay Pharmaceuticals, Inc.

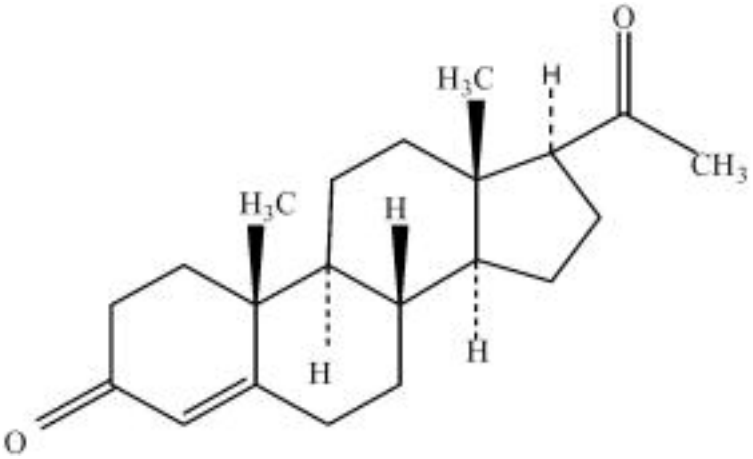
Rx Only
500032 Rev Jan 2008

WARNINGS

Progestins and estrogens should not be used for the prevention of cardiovascular disease. (See WARNINGS, Cardiovascular Disorders.)
The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5 years of treatment with oral conjugated estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) relative to placebo. (See CLINICAL PHARMACOLOGY, Clinical Studies.)
The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with oral conjugated estrogens plus medroxyprogesterone acetate relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. (See CLINICAL PHARMACOLOGY, Clinical Studies.)
Other doses of oral conjugated estrogens with medroxyprogesterone and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials. In the absence of comparable data and product-specific studies, the relevance of the WHI findings to other products has not been established. Therefore, the risks should be assumed to be similar for all estrogen and progestin products. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

DESCRIPTION

PROMETRIUM® (progesterone, USP) Capsules contain micronized progesterone for oral administration. Progesterone has a molecular weight of 314.47 and a molecular formula of $C_{21}H_{30}O_2$. Progesterone (pregn-4-ene-3, 20-dione) is a white or creamy white, odorless, crystalline powder practically insoluble in water, soluble in alcohol, acetone and dioxane and sparingly soluble in vegetable oils, stable in air, melting between 126° and 131°C. The structural formula is:



Progesterone is synthesized from a starting material from a plant source and is chemically identical to progesterone of human ovarian origin. PROMETRIUM Capsules are available in multiple strengths to afford dosage flexibility for optimum management. PROMETRIUM Capsules contain 100 mg or 200 mg micronized progesterone.
The inactive ingredients for PROMETRIUM Capsules 100 mg include: peanut oil NF, gelatin NF, glycerin USP, lecithin NF, titanium dioxide USP, D&C Yellow No. 10, and FD&C Red No. 40.
The inactive ingredients for PROMETRIUM Capsules 200 mg include: peanut oil NF, gelatin NF, glycerin USP, lecithin NF, titanium dioxide USP, D&C Yellow No. 10, and FD&C Yellow No. 6.

CLINICAL PHARMACOLOGY

PROMETRIUM Capsules are an oral dosage form of micronized progesterone which is chemically identical to progesterone of ovarian origin. The oral bioavailability of progesterone is increased through micronization.

Pharmacokinetics

Absorption: After oral administration of progesterone as a micronized soft-gelatin capsule formulation, maximum serum concentrations were attained within 3 hours. The absolute bioavailability of micronized progesterone is not known. Table 1 summarizes the mean pharmacokinetic parameters in postmenopausal women after five oral daily doses of PROMETRIUM Capsules 100 mg as a micronized soft-gelatin capsule formulation.

TABLE 1

Parameter	PROMETRIUM Capsules Daily Dose		
	100 mg	200 mg	300 mg
Cmax (ng/mL)	17.3 ± 21.9[a]	38.1 ± 37.8	60.6 ± 72.5
Tmax (hr)	1.5 ± 0.8	2.3 ± 1.4	1.7 ± 0.6
AUC (0-10) (ng•hr/mL)	43.3 ± 30.8	101.2 ± 66.0	175.7 ± 170.3

[a] Mean ± S.D.

Serum progesterone concentrations appeared linear and dose proportional following multiple dose administration of PROMETRIUM Capsules 100 mg over the dose range 100 mg/day to 300 mg/day in postmenopausal women. Although doses greater than 300 mg/day were not studied in females, serum concentrations from a study in male volunteers appeared linear and dose proportional between 100 mg/day and 400 mg/day. The pharmacokinetic parameters in male volunteers were generally consistent with those seen in postmenopausal women.

Distribution: Progesterone is approximately 96% to 99% bound to serum proteins, primarily to serum albumin (50% to 54%) and transcortin (43% to 48%).

Metabolism: Progesterone is metabolized primarily by the liver largely to pregnanediols and pregnanolones. Pregnanediols and pregnanolones are conjugated in the liver to glucuronide and sulfate metabolites. Progesterone metabolites which are excreted in the bile may be deconjugated and may be further metabolized in the gut via reduction, dehydroxylation, and epimerization.

Excretion: The glucuronide and sulfate conjugates of pregnanediol and pregnanolone are excreted in the bile and urine. Progesterone metabolites which are excreted in the bile may undergo enterohepatic recycling or may be excreted in the feces.

Special Populations: The pharmacokinetics of PROMETRIUM Capsules have not been assessed in low body weight or obese patients.

Race: There is insufficient information available from trials conducted with PROMETRIUM Capsules to compare progesterone pharmacokinetics in different racial groups.

Hepatic Insufficiency: No formal studies have evaluated the effect of hepatic disease on the disposition of progesterone. However, since progesterone is metabolized by the liver, use in patients with severe liver dysfunction or disease is contraindicated. (See **CONTRAINDICATIONS**.) If treatment with progesterone is indicated in patients with mild to moderate hepatic dysfunction, these patients should be monitored carefully.

Renal Insufficiency: No formal studies have evaluated the effect of renal disease on the disposition of progesterone. Since progesterone metabolites are eliminated mainly by the kidneys, PROMETRIUM Capsules should be used with caution and only with careful monitoring in patients with renal dysfunction. (See **PRECAUTIONS**.)

Food–Drug Interaction: Concomitant food ingestion increased the bioavailability of PROMETRIUM Capsules relative to a fasting state when administered to postmenopausal women at a dose of 200 mg.

Drug–Drug Interaction: The metabolism of progesterone by human liver microsomes was inhibited by ketoconazole (IC_{50}<0.1 μM). Ketoconazole is a known inhibitor of cytochrome P450 3A4, hence these data suggest that ketoconazole or other known inhibitors of this enzyme may increase the bioavailability of progesterone. The clinical relevance of the *in vitro* findings is unknown.

Coadministration of conjugated estrogens and PROMETRIUM Capsules to 29 postmenopausal women over a 12-day period resulted in an increase in total estrone concentrations (Cmax 3.68 ng/mL to 4.93 ng/mL) and total equilin concentrations (Cmax 2.27 ng/mL to 3.22 ng/mL) and a decrease in circulating 17β estradiol concentrations (Cmax 0.037 ng/mL to 0.030 ng/mL). The half-life of the conjugated estrogens was similar with coadministration of PROMETRIUM Capsules. Table 2 summarizes the pharmacokinetic parameters.

TABLE 2 Mean (± S.D.) Pharmacokinetic Parameters for Estradiol, Estrone, and Equilin Following Coadministration of Conjugated Estrogens 0.625 mg and PROMETRIUM Capsules 200 mg for 12 Days to Postmenopausal Women

	Conjugated Estrogens			**Conjugated Estrogens plus PROMETRIUM Capsules**		
Drug	**Cmax (ng/mL)**	**Tmax (hr)**	**AUC(0-24h) (ng•h/mL)**	**Cmax (ng/mL)**	**Tmax (hr)**	**AUC(0-24h) (ng•h/mL)**
Estradiol	0.037 ± 0.048	12.7 ± 9.1	0.676 ± 0.737	0.030 ± 0.032	17.32 ± 1.21	0.561 ± 0.572
Estrone Total[a]	3.68 ± 1.55	10.6 ± 6.8	61.3 ± 26.36	4.93 ± 2.07	7.5 ± 3.8	85.9 ± 41.2
Equilin Total[a]	2.27 ± 0.95	6.0 ± 4.0	28.8 ± 13.0	3.22 ± 1.13	5.3 ± 2.6	38.1 ± 20.2

[a] Total estrogens is the sum of conjugated and unconjugated estrogen.

Clinical Studies

Endometrial Protection: In a randomized, double-blind clinical trial, 358 postmenopausal women, each with an intact uterus, received treatment for up to 36 months. The treatment groups were: PROMETRIUM Capsules at the dose of 200 mg/day for 12 days per 28-day cycle in combination with conjugated estrogens 0.625 mg/day (n=120); conjugated estrogens 0.625 mg/day only (n=119); or placebo (n=119). The subjects in all three treatment groups were primarily Caucasian women (87% or more of each group). The results for the incidence of endometrial hyperplasia in women receiving up to 3 years of treatment are shown in Table 3. A comparison of the PROMETRIUM Capsules plus conjugated estrogens treatment group to the conjugated estrogens only group showed a significantly lower rate of hyperplasia (6% combination product vs. 64% estrogen alone) in the PROMETRIUM Capsules plus conjugated estrogens treatment group throughout 36 months of treatment.

TABLE 3 Incidence of Endometrial Hyperplasia in Women Receiving 3 Years of Treatment

Endometrial Diagnosis	**Treatment Group**					
	Conjugated Estrogens 0.625 mg + PROMETRIUM Capsules 200 mg (cyclical)		**Conjugated Estrogens 0.625 mg (only)**		**Placebo**	
	Number of patients	**% of patients**	**Number of patients**	**% of patients**	**Number of patients**	**% of patients**
	n=117		**n=115**		**n=116**	
HYPERPLASIA[a]	7	6	74	64	3	3
Adenocarcinoma	0	0	0	0	1	1
Atypical hyperplasia	1	1	14	12	0	0
Complex hyperplasia	0	0	27	23	1	1
Simple hyperplasia	6	5	33	29	1	1

[a]Most advanced result to least advanced result:
Adenocarcinoma > atypical hyperplasia > complex hyperplasia > simple hyperplasia

The times to diagnosis of endometrial hyperplasia over 36 months of treatment are shown in Figure 1. This figure illustrates graphically that the proportion of patients with hyperplasia was significantly greater for the conjugated estrogens group (64%) compared to the conjugated estrogens plus PROMETRIUM Capsules group (6%).

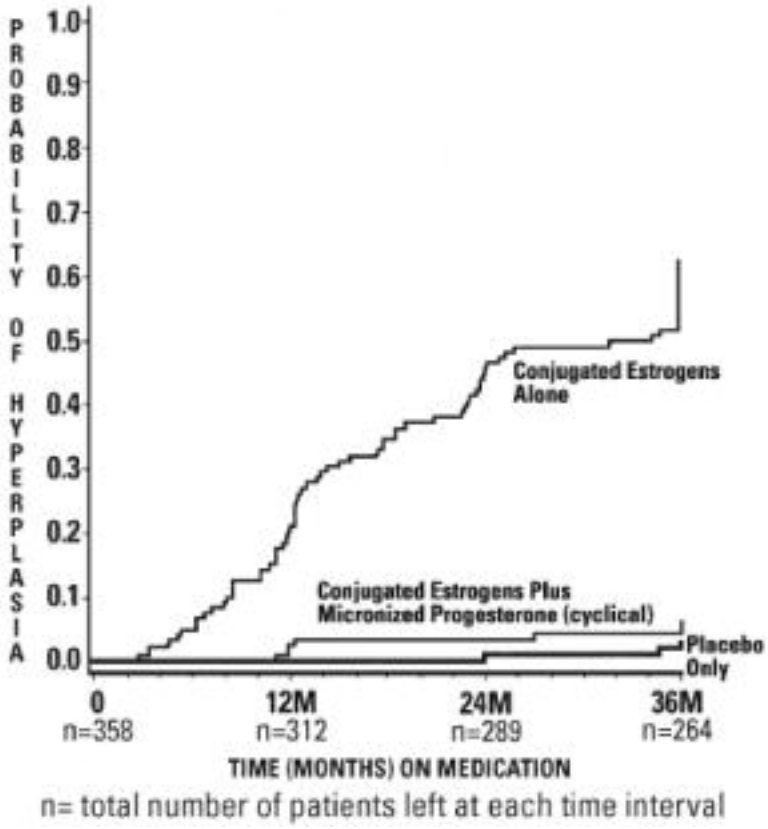


Figure 1 Time to Hyperplasia in Women Receiving up to 36 Months of Treatment

The discontinuation rates due to hyperplasia over the 36 months of treatment are as shown in Table 4. For any degree of hyperplasia, the discontinuation rate for patients who received conjugated estrogens plus PROMETRIUM Capsules was similar to that of the placebo only group, while the discontinuation rate for patients who received conjugated estrogens alone was significantly higher. Women who permanently discontinued treatment due to hyperplasia were similar in demographics to the overall study population.

TABLE 4 Discontinuation Rate Due to Hyperplasia Over 36 Months of Treatment

Most Advanced Biopsy Result Through 36 Months of Treatment	**Treatment Group**					
	Conjugated Estrogens + PROMETRIUM Capsules (cyclical)		**Conjugated Estrogens (only)**		**Placebo**	
	n=120		**n=119**		**n=119**	
	Number of patients	**% of patients**	**Number of patients**	**% of patients**	**Number of patients**	**% of patients**
Adenocarcinoma	0	0	0	0	1	1
Atypical hyperplasia	1	1	10	8	0	0
Complex hyperplasia	0	0	21	18	1	1
Simple hyperplasia	1	1	13	11	0	0

In the same 3-year clinical trial, postmenopausal women were treated with PROMETRIUM Capsules in combination with conjugated estrogens, conjugated estrogens only, or placebo. There was no statistically significant difference between the PROMETRIUM Capsules plus conjugated estrogens group and the conjugated estrogens only group in increases of HDL-C and triglycerides, or in decreases of LDL-C. The changes observed in lipid profiles are shown in Table 5.

TABLE 5 Mean Changes from Baseline in Lipid Profiles After 36 Months of Treatment

Parameter	Treatment Group Mean (Mean % Change)					
	Conjugated Estrogens 0.625 mg + PROMETRIUM Capsules 200 mg (cyclical)[a]		Conjugated Estrogens 0.625 mg (only)		Placebo	
	n= 176 to 177[b]		n=171 to 173[b]		n=171	
	Mean Change	Mean % Change	Mean Change	Mean % Change	Mean Change	Mean % Change
LIPID PROFILE						
HDL-C(mmol/L)	0.07	5.1	0.10	7.2	-0.05	-2
LDL-C(mmol/L)	-0.43	-11.8	-0.36	-9.5	-0.14	-2.9
Cholesterol (mmol/L)	-0.26	-4.0	-0.22	-3.6	-0.15	-1.8
Triglyceride (mmol/L)[c]	0.20	17.8	0.15	13.7	0.01	0.6

[a] There are no significant changes ($p<0.05$) from conjugated estrogens values.

[b] Number of subjects (n) varies by parameter.

[c] Computed from log transformed data.

Secondary Amenorrhea: In a single-center, randomized, double-blind clinical study that included premenopausal women with secondary amenorrhea for at least 90 days, administration of 10 days of PROMETRIUM Capsules therapy resulted in 80% of women experiencing withdrawal bleeding within 7 days of the last dose of PROMETRIUM Capsules, 300 mg/day (n=20), compared to 10% of women experiencing withdrawal bleeding in the placebo group (n=21).

The rate of secretory transformation was evaluated in a multicenter, randomized, double-blind clinical study in estrogen-primed postmenopausal women. PROMETRIUM Capsules administered orally for 10 days at 400 mg/day (n=22) induced complete secretory changes in the endometrium in 45% of women compared to 0% in the placebo group (n=23).

Women's Health Initiative Studies

The Women's Health Initiative (WHI) enrolled a total of 27,000 predominantly healthy postmenopausal women to assess the risks and benefits of either the use of oral 0.625 mg conjugated estrogens (CE) per day alone or the use of oral 0.625 mg conjugated estrogens plus 2.5 mg medroxyprogesterone acetate (MPA) per day compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome studied. A “global index” included the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, or death due to other cause. The study did not evaluate the effects of CE or CE/MPA on menopausal symptoms.

The CE/MPA substudy was stopped early because, according to the predefined stopping rule, the increased risk of breast cancer and cardiovascular events exceeded the specified benefits included in the “global index.” Results of the CE/MPA substudy, which included 16,608 women (average age of 63 years, range 50 to 79; 83.9% White, 6.5% Black, 5.5% Hispanic), after an average follow-up of 5.2 years are presented in Table 6 below.

TABLE 6 Relative and Absolute Risk Seen in the CE/MPA Substudy of WHI[a]

Event[c]	Relative Risk CE/MPA vs. placebo at 5.2 Years (95% CI*)	Placebo n = 8102	CE/MPA n = 8506
		Absolute Risk per 10,000 Women-years	
CHD events	1.29 (1.02-1.63)	30	37
Non-fatal MI	*1.32 (1.02-1.72)*	*23*	*30*
CHD death	*1.18 (0.70-1.97)*	*6*	*7*
Invasive breast cancer[b]	1.26 (1.00-1.59)	30	38
Stroke	1.41 (1.07-1.85)	21	29
Pulmonary embolism	2.13 (1.39-3.25)	8	16

Colorectal cancer	0.63 (0.43-0.92)	16	10
Endometrial cancer	0.83 (0.47-1.47)	6	5
Hip fracture	0.66 (0.45-0.98)	15	10
Death due to causes other than the events above	0.92 (0.74-1.14)	40	37
Global Index [c]	1.15 (1.03-1.28)	151	170
Deep vein thrombosis [d]	2.07 (1.49-2.87)	13	26
Vertebral fractures [d]	0.66 (0.44-0.98)	15	9
Other osteoporotic fractures [d]	0.77 (0.69-0.86)	170	131

[a] adapted from *JAMA*, 2002; 288:321-333

[b] includes metastatic and non-metastatic breast cancer with the exception of *in situ* breast cancer

[c] a subset of the events was combined in a “global index,” defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes

[d] not included in Global Index

* nominal confidence intervals unadjusted for multiple looks and multiple comparisons

For those outcomes included in the "global index," the absolute excess risks per 10,000 women-years in the group treated with CE/MPA were 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, while the absolute risk reductions per 10,000 women-years were 6 fewer colorectal cancers and 5 fewer hip fractures. The absolute excess risk of events included in the “global index” was 19 per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality. (See **BOXED WARNINGS, WARNINGS**, and **PRECAUTIONS**.)

Women's Health Initiative Memory Study
The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47% were age 65 to 69 years, 35% were 70 to 74 years, and 18% were 75 years of age and older) to evaluate the effects of CE/MPA (0.625 mg conjugated estrogens plus 2.5 mg medroxyprogesterone acetate) on the incidence of probable dementia (primary outcome) compared with placebo.

After an average follow-up of 4 years, 40 women in the estrogen/progestin group (45 per 10,000 women-years) and 21 in the placebo group (22 per 10,000 women-years) were diagnosed with probable dementia. The relative risk of probable dementia in the hormone therapy group was 2.05 (95% CI, 1.21 to 3.48) compared to placebo. Differences between groups became apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women. (See **BOXED WARNINGS and WARNINGS, Dementia**.)

INDICATIONS AND USAGE
PROMETRIUM Capsules are indicated for use in the prevention of endometrial hyperplasia in nonhysterectomized postmenopausal women who are receiving conjugated estrogens tablets. They are also indicated for use in secondary amenorrhea.

CONTRAINDICATIONS
PROMETRIUM Capsules should not be used in women with any of the following conditions:

1. **PROMETRIUM Capsules should not be used in patients with known hypersensitivity to its ingredients. PROMETRIUM Capsules contain peanut oil and should never be used by patients allergic to peanuts.**
2. Undiagnosed abnormal genital bleeding.
3. Known, suspected, or history of cancer of the breast.
4. Active deep vein thrombosis, pulmonary embolism or history of these conditions.
5. Active or recent (e.g., within the past year) arterial thromboembolic disease (e.g., stroke, myocardial infarction).
6. Liver dysfunction or disease.
7. Known or suspected pregnancy. There is no indication for PROMETRIUM Capsules in pregnancy. There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins from oral contraceptives inadvertently during early pregnancy. (See **PRECAUTIONS**.)

WARNINGS
See **BOXED WARNINGS**.

Cardiovascular Disorders
Estrogen with progestin therapy has been associated with an increased risk of cardiovascular events such as myocardial infarction and stroke, as well as venous thrombosis and pulmonary embolism (venous thromboembolism or VTE). Should any of these occur or be suspected, estrogen with progestin should be discontinued immediately.
Risk factors for arterial vascular disease (e.g., hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (e.g., personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately.
Coronary Heart Disease and Stroke: In the Women's Health Initiative (WHI) study, an increase in the number of strokes was observed in women receiving CE compared to placebo.

In the CE/MPA substudy of WHI, an increased risk of coronary heart disease (CHD) events (defined as nonfatal myocardial infarction and CHD death) was observed in women receiving CE/MPA compared to women receiving placebo (37 vs. 30 per 10,000 women-years). The increase in risk was observed in year one and persisted. (See **CLINICAL PHARMACOLOGY, Clinical Studies**.)

In the same substudy of WHI, an increased risk of stroke was observed in women receiving CE/MPA compared to women receiving placebo (29 vs. 21 per 10,000 women-years). The increase in risk was observed after the first year and persisted. (See **CLINICAL PHARMACOLOGY, Clinical Studies**.)

In postmenopausal women with documented heart disease (n = 2,763, average age 66.7 years) a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study; HERS) treatment with CE/MPA (0.625 mg/2.5 mg per day) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE/MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE/MPA-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand three hundred and twenty one women from the original HERS trial agreed to participate in an open-label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE/MPA group and the placebo group in HERS, HERS II, and overall.

Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risks of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis.

Venous Thromboembolism (VTE.): In the Women's Health Initiative (WHI) study, an increase in VTE was observed in women receiving CE compared to placebo.

In the CE/MPA substudy of WHI, a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism, was observed in women receiving CE/MPA compared to women receiving placebo. The rate of VTE was 34 per 10,000 women-years in the CE/MPA group compared to 16 per 10,000 women-years in the placebo group. The increase in VTE risk was observed during the first year and persisted. (See **CLINICAL PHARMACOLOGY, Clinical Studies**.)

If feasible, estrogens with progestins should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

Breast Cancer
The use of estrogens and progestins by postmenopausal women has been reported to increase the risk of breast cancer. The most important randomized clinical trial providing information about this issue is the Women's Health Initiative (WHI) substudy of CE/MPA. (See **CLINICAL PHARMACOLOGY, Clinical Studies**.) The results from observational studies are generally consistent with those of the WHI clinical trial and report no significant variation in the risk of breast cancer among different estrogens or progestins, doses, or routes of administration.
The CE/MPA substudy of WHI reported an increased risk of breast cancer in women who took CE/MPA for a mean follow-up of 5.6 years. Observational studies have also reported an increased risk for estrogen/progestin combination therapy, and a smaller increased risk for estrogen alone therapy, after several years of use. In the WHI trial and from observational studies, the excess risk increased with duration of use. From observational studies, the risk appeared to return to baseline in about five years after stopping treatment. In addition, observational studies suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen/progestin combination therapy as compared to estrogen alone therapy.
In the CE/MPA substudy, 26% of the women reported prior use of estrogen alone and/or estrogen/progestin combination hormone therapy. After a mean follow-up of 5.6 years during the clinical trial, the overall relative risk of invasive breast cancer was 1.24 (95% confidence interval 1.01-1.54), and the overall absolute risk was 41 vs. 33 cases per 10,000 women-years, for CE/MPA compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the

absolute risk was 46 vs. 25 cases per 10,000 women-years, for CE/MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 vs. 36 cases per 10,000 women-years for CE/MPA compared with placebo. In the same substudy, invasive breast cancers were larger and diagnosed at a more advanced stage in the CE/MPA group compared with the placebo group. Metastatic disease was rare with no apparent difference between the two groups. Other prognostic factors such as histologic subtype, grade and hormone receptor status did not differ between the groups.
The use of estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

Vision Disorders
Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

Dementia
In the Women's Health Initiative Memory Study (WHIMS), 4,532 generally healthy postmenopausal women 65 years of age and older were studied, of whom 35% were 70 to 74 years of age and 18% were 75 or older. After an average follow-up of 4 years, 40 women being treated with CE/MPA (1.8%, n = 2,229) and 21 women in the placebo group (0.9%, n = 2,303) received diagnoses of probable dementia. The relative risk for CE/MPA vs. placebo was 2.05 (95% confidence interval 1.21 – 3.48), and was similar for women with and without histories of menopausal hormone use before WHIMS. The absolute risk of probable dementia for CE/MPA vs. placebo was 45 vs. 22 cases per 10,000 women-years, and the absolute excess risk for CE/MPA was 23 cases per 10,000 women-years. It is unknown whether these findings apply to younger postmenopausal women. (See **CLINICAL PHARMACOLOGY, Clinical Studies** and **PRECAUTIONS, Geriatric Use**.)

PRECAUTIONS
Use of estrogens with a progestin may increase the risk of breast cancer compared to estrogen alone.

Ovarian Cancer
The CE/MPA substudy of WHI reported that estrogen plus progestin increased the risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE/MPA vs. placebo was 1.58 (95% confidence interval 0.77 – 3.24) but was not statistically significant. The absolute risk for CE/MPA vs. placebo was 4.2 vs. 2.7 cases per 10,000 women-years. In some epidemiologic studies, the use of estrogen alone, in particular for ten or more years, has been associated with an increased risk of ovarian cancer. Other epidemiologic studies have not found these associations.

General
1. The pretreatment physical examination should include special reference to breast and pelvic organs, as well as Papanicolaou smear.

2. Because progesterone may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation.

3. In cases of breakthrough bleeding, as in any cases of irregular vaginal bleeding, nonfunctional causes should be considered. In cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated.

4. Patients who have a history of clinical depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

5. Further studies are needed to determine any possible influence of prolonged progestin therapy on pituitary, ovarian, adrenal, hepatic or uterine functions.

6. Although concomitant use of conjugated estrogens and PROMETRIUM Capsules did not result in a decrease in glucose tolerance, diabetic patients should be carefully observed while receiving estrogen-progestin therapy.

7. The pathologist should be advised of progestin therapy when relevant specimens are submitted.

8. Because of the occurrence of thrombotic disorders (thrombophlebitis, pulmonary embolism, retinal thrombosis, and cerebrovascular disorders) in patients taking estrogen-progestin combinations, the healthcare provider should be alert to the earliest manifestation of these disorders.

9. Transient dizziness may occur in some patients. Use caution when driving a motor vehicle or operating machinery. A small percentage of women may experience the following symptoms upon initial therapy: extreme dizziness and/or drowsiness, blurred vision, slurred speech, difficulty walking, loss of consciousness, vertigo, confusion, disorientation, feeling drunk, and shortness

of breath. For these women, consultation with their healthcare provider regarding their treatment is advised. Bedtime dosing may alleviate these symptoms.

10. Rare instances of syncope and hypotension of possible orthostatic origin have been observed in patients taking PROMETRIUM Capsules.

Information for the Patient
See accompanying Patient Insert.
General: This product contains peanut oil and should not be used if you are allergic to peanuts.

Drug/Laboratory Test Interactions
The following laboratory results may be altered by the use of estrogen-progestin combination drugs:
- Increased sulfobromophthalein retention and other hepatic function tests.

- Coagulation tests: increase in prothrombin factors VII, VIII, IX and X.

- Metyrapone test.

- Pregnanediol determination.

- Thyroid function: increase in PBI, and butanol extractable protein bound iodine and decrease in T3 uptake values.

Fasting and 2-hour plasma insulin and glucose levels following an oral glucose tolerance test (OGTT) and fibrinogen levels were measured in patients receiving PROMETRIUM Capsules at a dose of 200 mg/day for 12 days per 28-day cycle in combination with conjugated estrogens 0.625 mg/day (n=120). Table 7 summarizes these data. Plasma insulin levels 2 hours post-OGTT were decreased from baseline. The fasting plasma glucose and fasting plasma insulin levels were also decreased from baseline. Glucose levels 2 hours post-OGTT were increased slightly. There was no effect on fibrinogen levels.
For information on changes in lipid profile, see the **Clinical Studies subsection, Table 5**.
TABLE 7 Mean Changes from Baseline in Insulin and Glucose Levels After 36 Months of Treatment

Parameter		**Treatment Group Mean (Mean % Change)**					
		Conjugated Estrogens 0.625 mg + PROMETRIUM Capsules 200 mg (cyclical)[a]		**Conjugated Estrogens 0.625 mg (only)**		**Placebo**	
		n= 173 to 176[b]		**n=170 to 172[b]**		**n=171**	
		Mean Change	**Mean % Change**	**Mean Change**	**Mean % Change**	**Mean Change**	**Mean % Change**
OGTT Insulin (pmol/L)	fasting	-2.2	-6.2	-1.1	-3.2	5.1	14.2
	2 hours	-45.2	-14.5	-23.9	-7.9	-29.7	-9.1
Glucose (mg/dL)	fasting	-3.0	-2.9	-2.7	-2.7	-1.0	-0.9
	2 hours	3.6	5.2	5.0	7.8	2.1	3.9

[a] There are no significant changes ($p<0.05$) from conjugated estrogens values.

[b] Number of subjects (n) varies by parameter.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Progesterone has not been tested for carcinogenicity in animals by the oral route of administration. When implanted into female mice, progesterone produced mammary carcinomas, ovarian granulosa cell tumors and endometrial stromal sarcomas. In dogs, long-term intramuscular injections produced nodular hyperplasia and benign and malignant mammary tumors. Subcutaneous or intramuscular injections of progesterone decreased the latency period and increased the incidence of mammary tumors in rats previously treated with a chemical carcinogen.
Progesterone did not show evidence of genotoxicity in *in vitro* studies for point mutations or for chromosomal damage. *In vivo* studies for chromosome damage have yielded positive results in mice at oral doses of 1000 mg/kg and 2000 mg/kg. Exogenously administered progesterone has been shown to inhibit ovulation in a number of species and it is expected that high doses given for an extended duration would impair fertility until the cessation of treatment.

Pregnancy Category B
Reproductive studies have been performed in mice at doses up to 9 times the human oral dose, in rats at doses up to 44 times the human oral dose, in rabbits at a dose of 10 mcg/day delivered locally within the uterus by an implanted device, in guinea pigs at doses of approximately one-half the human oral dose and in rhesus monkeys at doses approximately the human dose, all based on body surface area, and have revealed little or no evidence of impaired fertility or harm to the fetus due to progesterone.
Rare cases of congenital anomalies including cleft palate, cleft lip, hypospadia, ventricular septal defect, patent ductus arteriosus, and other congenital heart defects have been reported in the infants of women using progesterone, including PROMETRIUM Capsules, in early pregnancy. Definitive causality has not been established. Rare instances of fetal death and spontaneous abortion have been reported in pregnant women prescribed PROMETRIUM Capsules for unapproved indications including the prevention of such outcomes. Studies in humans cannot rule out the possibility of harm. Therefore, PROMETRIUM Capsules should be used during pregnancy only if indicated. (See **CONTRAINDICATIONS**.)

Nursing Mothers
The administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk. Detectable amounts of progestin have been identified in the milk of nursing mothers receiving progestins. Caution should be exercised when PROMETRIUM Capsules are administered to a nursing woman.

Pediatric Use
PROMETRIUM Capsules are not indicated in children.

Geriatric Use
Clinical studies of PROMETRIUM Capsules did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.
In the Women's Health Initiative Memory Study, including 4,532 women 65 years of age and older, followed for an average of 4 years, 82% (n = 3,729) were 65 to 74 while 18% (n = 803) were 75 and over. Most women (80%) had no prior hormone therapy use. Women treated with conjugated estrogens plus medroxyprogesterone acetate were reported to have a two-fold increase in the risk of developing probable dementia. Alzheimer's disease was the most common classification of probable dementia in both the conjugated estrogens plus medroxyprogesterone acetate group and the placebo group. Ninety percent of the cases of probable dementia occurred in the 54% of women that were older than 70. (See **WARNINGS, Dementia**.)

ADVERSE REACTIONS
See **BOXED WARNINGS, WARNINGS**, and **PRECAUTIONS**.
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximate rates.
Endometrial Protection: Table 8 lists adverse experiences which were reported in ≥2% of patients (regardless of relationship to treatment) who received cyclic PROMETRIUM Capsules, 200 mg daily (12 days per calendar month cycle) with daily 0.625 mg conjugated estrogen, in a multicenter, randomized, double-blind, placebo-controlled clinical trial in 875 postmenopausal women.
TABLE 8 Adverse Experiences (≥2%) Reported in an 875 Patient Placebo-Controlled Trial in Postmenopausal Women Over a 3-Year Period [Percentage (%) of Patients Reporting]

	PROMETRIUM Capsules 200 mg with Conjugated Estrogens 0.625 mg	**Conjugated Estrogens 0.625 mg (only)**	**Placebo**
	(n=178)	**(n=175)**	**(n=174)**
Headache	31	30	27
Breast Tenderness	27	16	6
Joint Pain	20	22	29
Depression	19	18	12
Dizziness	15	5	9
Abdominal Bloating	12	10	5
Hot Flashes	11	14	35
Urinary Problems	11	10	9
Abdominal Pain	10	13	10

Vaginal Discharge	10	10	3
Nausea / Vomiting	8	6	7
Worry	8	5	4
Chest Pain	7	4	5
Diarrhea	7	7	4
Night Sweats	7	5	17
Breast Pain	6	6	2
Swelling of Hands and Feet	6	9	9
Vaginal Dryness	6	8	10
Constipation	3	3	2
Breast Carcinoma	2	<1	<1
Breast Excisional Biopsy	2	1	<1
Cholecystectomy	2	<1	<1

Secondary Amenorrhea: Table 9 lists adverse experiences which were reported in ≥5% of patients receiving PROMETRIUM Capsules, 400 mg/day, in a multicenter, randomized, double-blind, placebo-controlled clinical trial in estrogen-primed (6 weeks) postmenopausal women receiving conjugated estrogens 0.625 mg/day and cyclic (10 days per calendar month cycle) PROMETRIUM Capsules at a dose of 400 mg/day, for three cycles.

TABLE 9 Adverse Experiences (≥5%) Reported in Patients Using 400 mg/day in a Placebo-Controlled Trial in Estrogen-Primed Postmenopausal Women

Adverse Experience	**PROMETRIUM Capsules 400 mg**	**Placebo**
	n=25	**n=24**
	Percentage (%) of Patients	
Fatigue	8	4
Headache	16	8
Dizziness	24	4
Abdominal Distention (Bloating)	8	8
Abdominal Pain (Cramping)	20	13
Diarrhea	8	4
Nausea	8	0
Back Pain	8	8
Musculoskeletal Pain	12	4
Irritability	8	4
Breast Pain	16	8
Infection Viral	12	0
Coughing	8	0

The most common adverse experiences reported in ≥5% of patients in all PROMETRIUM Capsules dosage groups studied in this trial (100 mg/day to 400 mg/day) were: dizziness (16%), breast pain (11%), headache (10%), abdominal pain (10%), fatigue (9%), viral infection (7%), abdominal distention (6%), musculoskeletal pain (6%), emotional lability (6%), irritability (5%), and upper respiratory tract infection (5%).

Other adverse events reported in <5% of patients taking PROMETRIUM Capsules include:

Administration Site Conditions: edema, edema peripheral

Blood and Lymphatic System: lymphadenopathy

Cardiac Disorders: angina pectoris, palpitation

Ear and Labyrinth Disorders: earache

Eye Disorders: abnormal vision

Gastrointestinal System Disorders: constipation, dry mouth, dyspepsia, gastroenteritis, hemorrhagic rectum, hiatus hernia, vomiting

General Disorders: chest pain, fever

Infections: abscess, herpes simplex

Injury, Poisoning and Procedural Complications: accidental injury

Musculoskeletal and Connective Tissue Disorders: arthritis, leg cramps, muscle disorder, myalgia
Nervous System Disorders: hypertonia, impaired concentration, somnolence, speech disorder
Psychiatric Disorders: anxiety, confusion, insomnia, personality disorder
Renal and Urinary Disorders: urinary tract infection
Reproductive System Disorders: fungal vaginitis, leukorrhea, uterine fibroid, vaginal dryness, vaginitis
Respiratory System Disorders: bronchitis, nasal congestion, pharyngitis, pneumonitis, sinusitis
Skin and Subcutaneous Tissue Disorders: acne, verruca, wound debridement
Vascular Disorders: hypertension
The following adverse experiences have been reported with PROMETRIUM Capsules in other U.S. clinical trials: increased sweating, asthenia, tooth disorder, anorexia, increased appetite, nervousness, and breast enlargement.
In addition to the adverse events observed in clinical trials, the following spontaneous adverse events have been reported during the marketing of PROMETRIUM Capsules.
Cardiac Disorders: circulatory collapse, tachycardia
Congenital, Familial, and Genetic Disorders: cleft lip, cleft palate, congenital heart disease, patent ductus arteriosus, ventricular septal defect
Ear and Labyrinth Disorders: tinnitus, vertigo
Eye Disorders: blurred vision, diplopia, visual disturbance
Gastrointestinal Disorders: acute pancreatitis, dysphagia, swollen tongue
General Disorders and Administration Site Conditions: abnormal gait, difficulty walking, feeling abnormal, feeling drunk
Hepatobiliary Disorders: cholestasis, cholestatic hepatitis, jaundice, hepatitis, hepatic failure, hepatic necrosis, increased liver function tests
Immune System Disorders: anaphylactic reaction, hypersensitivity
Investigations: alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyl transferase increased, hepatic enzyme increased, blood glucose increased, weight decreased, weight increased
Musculoskeletal Disorders: arthralgia, muscle cramp
Neoplasms Benign, Malignant, and Unspecified: endometrial carcinoma
Nervous System Disorders: convulsion, depressed consciousness, dysarthria, loss of consciousness, paresthesia, sedation, stupor, syncope (with and without hypotension), transient ischemic attack
Pregnancy, Puerperium, and Perinatal Conditions: intra-uterine death, spontaneous abortion
Psychiatric Disorders: aggression, depersonalization, disorientation, suicidal ideation,
Reproductive System and Breast Disorders: menorrhagia, menstrual disorder, metrorrhagia, ovarian cyst
Respiratory, Thoracic, and Mediastinal Disorders: asthma, choking, dyspnea, face edema, throat tightness
Skin and Subcutaneous Tissue Disorders: alopecia, pruritus, urticaria
Vascular Disorders: hypertension, hypotension
The following additional adverse experiences have been observed in women taking estrogen and/or progestins in general: breakthrough bleeding, spotting, change in menstrual flow, amenorrhea, changes in weight (increase or decrease), changes in the cervical squamo-columnar junction and cervical secretions, cholestatic jaundice, anaphylactoid reactions and anaphylaxis, rash (allergic) with and without pruritus, melasma or chloasma, that may persist when drug is discontinued, dysmenorrhea, increase in size of uterine leiomyomata, ovarian cancer, endometrial hyperplasia, endometrial cancer, galactorrhea, nipple discharge, increased incidence of gallbladder disease, enlargement of hepatic hemangiomas, erythema multiforme, erythema nodosum, hirsutism, hemorrhagic eruption, intolerance to contact lenses, migraine, chorea, reduced carbohydrate tolerance, aggravation of porphyria, changes in libido, hypocalcemia, angioedema, exacerbation of asthma, increased triglycerides.

OVERDOSAGE

No studies on overdosage have been conducted in humans. In the case of overdosage, PROMETRIUM Capsules should be discontinued and the patient should be treated symptomatically.

DOSAGE AND ADMINISTRATION

Prevention of Endometrial Hyperplasia: PROMETRIUM Capsules should be given as a single daily dose at bedtime, 200 mg orally for 12 days sequentially per 28-day cycle, to postmenopausal women with a uterus who are receiving daily conjugated estrogens tablets.
Secondary Amenorrhea: PROMETRIUM Capsules may be given as a single daily dose of 400 mg at bedtime for 10 days.
Some women may experience difficulty swallowing PROMETRIUM Capsules. For these women, PROMETRIUM Capsules should be taken with a glass of water while in the standing position.

HOW SUPPLIED

PROMETRIUM® (progesterone, USP) Capsules 100 mg are round, peach-colored capsules branded with black imprint “SV.”
NDC 0032-1708-01 (Bottle of 100)
PROMETRIUM® (progesterone, USP) Capsules 200 mg are oval, pale yellow-colored capsules branded with black imprint “SV2.”
NDC 0032-1711-01 (Bottle of 100)

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].
Protect from excessive moisture.
Dispense in tight, light-resistant container as defined in USP/NF, accompanied by a Patient Insert.
Keep out of reach of children.
Manufactured by:
Catalent Pharma Solutions
St. Petersburg, FL 33716
Marketed by:
Solvay Pharmaceuticals, Inc.
Marietta, GA 30062

500032 Rev Jan 2008
500033 Rev Jan 2008

PATIENT INFORMATION
(Updated 02 Jan 2008)
PROMETRIUM® (progesterone, USP)
Capsules 100 mg
Capsules 200 mg
Rx only

Read this PATIENT INFORMATION before you start taking PROMETRIUM® Capsules and read what you get each time you refill PROMETRIUM Capsules, because there may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT PROMETRIUM CAPSULES (A Progesterone Hormone)?

- Progesterone with or without estrogens should not be used to prevent heart attacks or heart disease.
- Using estrogens with or without progestins may increase your chances of getting heart attacks, strokes, breast cancer, and blood clots. Using estrogens with progestins may increase your risk of dementia. You and your healthcare provider should talk regularly about whether you still need treatment with PROMETRIUM Capsules.

THIS PRODUCT CONTAINS PEANUT OIL AND SHOULD NOT BE USED IF YOU ARE ALLERGIC TO PEANUTS.

WHAT IS PROMETRIUM CAPSULES?

PROMETRIUM Capsules contain the female hormone called progesterone.

What is PROMETRIUM Capsules used for?

Treatment of Menstrual Irregularities

PROMETRIUM Capsules are used for the treatment of secondary amenorrhea (absence of menstrual periods in women who have previously had a menstrual period) due to a decrease in progesterone. When you do not produce enough progesterone, menstrual irregularities can occur. If your healthcare provider has determined your body does not produce enough progesterone on its own, PROMETRIUM Capsules may be prescribed to provide the progesterone you need.

Protection of the Endometrium (Lining of the Uterus)

PROMETRIUM Capsules are used in combination with estrogen-containing medications in postmenopausal women with a uterus. Taking estrogens alone increases the chance of developing a condition called endometrial hyperplasia, that may lead to cancer of the lining of the uterus. In general, the addition of a progestin is recommended for women with a uterus to reduce the chance of getting cancer of the uterus.

Who should not take PROMETRIUM Capsules?

Do not start taking PROMETRIUM Capsules if you:

- **are allergic to peanuts.**
- **are allergic to progesterone, progesterone-like drugs, or any of the inactive ingredients in the capsules.** See the end of this leaflet for a list of ingredients in PROMETRIUM Capsules.
- **are pregnant or suspect that you are pregnant.**
- **have or have had blood clots in the legs, lungs, eyes, brain, or elsewhere.**
- **have liver disease.**

- **have known or suspected cancer of the breast or reproductive organs.**

- **have unusual bleeding from the vagina which has not been evaluated by your healthcare provider.**

- **have a miscarriage and your healthcare provider suspects some tissue is still in the uterus.**

- **are nursing.**

Tell your healthcare provider:
- **if you are breastfeeding.** The hormones in PROMETRIUM Capsules can pass into your milk.

- **about all of your medical problems.** Your healthcare provider may need to check you more carefully if you have certain conditions, such as diabetes, asthma (wheezing), epilepsy (seizures), migraine, endometriosis, lupus, problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood.

- **about all the medicines you take.** This includes prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may affect how PROMETRIUM Capsules works. PROMETRIUM Capsules may also affect how your other medicines work.

How should I take PROMETRIUM Capsules?
1. Prevention of Endometrial Hyperplasia: Postmenopausal women with a uterus who are taking estrogens should take a single daily dose of 200 mg PROMETRIUM Capsules at bedtime for 12 continuous days per 28-day cycle.

2. Secondary Amenorrhea: PROMETRIUM Capsules may be given as a single daily dose of 400 mg at bedtime for 10 days.

3. **PROMETRIUM Capsules are to be taken at bedtime as some women become very drowsy* and/or dizzy* after taking PROMETRIUM Capsules. In a small percentage of these women, these effects may be increased including blurred vision, difficulty speaking, difficulty walking, and feeling abnormal. If you experience these symptoms, discuss them with your healthcare provider immediately. Taking PROMETRIUM Capsules at bedtime may minimize the impact of these symptoms.**

* Use caution when driving a motor vehicle or operating machinery as dizziness or drowsiness may occur.
If you experience difficulty in swallowing PROMETRIUM Capsules, it is recommended that you take your daily dose at bedtime with a glass of water while in the standing position.
What are the risks associated with PROMETRIUM Capsules?
- ***Risk to the Fetus:*** Rare cases of cleft palate, cleft lip, hypospadia, and congenital heart defects have been reported in the infants of women using progesterone, including PROMETRIUM Capsules during early pregnancy. Although it is not clear that these events were drug related, you should check with your healthcare provider about the risks to your unborn child of any medication taken during pregnancy.

- ***Abnormal Blood Clotting:*** Use of progestational drugs has been associated with changes in the blood-clotting system. These changes allow the blood to clot more easily, possibly allowing clots to form in the bloodstream. If blood clots do form in your bloodstream, they can cut off the blood supply to vital organs, causing serious problems. These problems may include a stroke (by cutting off blood to part of the brain), a heart attack (by cutting off blood to part of the heart), a pulmonary embolus (by cutting off blood to part of the lungs), visual loss or blindness (by cutting off blood vessels in the eye), or other problems. Any of these conditions may cause death or serious long-term disability. Call your healthcare provider immediately if you suspect you have any of these conditions. He or she may advise you to stop using this drug.

- ***Eye Abnormalities:*** Discontinue medication and call your healthcare provider immediately if you experience sudden partial or complete loss of vision, blurred vision, or sudden onset of bulging eyes, double vision, or migraine.

What are the possible side effects of PROMETRIUM Capsules?
Consult your healthcare provider if you experience any of the side effects mentioned below or other side effects.
SIDE EFFECTS REPORTED IN STUDIES OF PATIENTS AT DOSES OF 100 MG/DAY TO 400 MG/DAY:
Blood and Lymphatic System: swelling of the lymph nodes
Cardiovascular System: high blood pressure, hot flashes, pounding or racing of the heart
Digestive System: bloating, constipation, diarrhea, dry mouth, heartburn, indigestion, nausea/vomiting
General Disorders: abdominal pain (cramping), back pain, chest pain, fatigue, fever, fluid retention, headache, intestinal pain, stomach pain, swelling, swelling of the legs and arms
Infections: bronchitis, fungal vaginal infection, infections, inflammation of the vagina, upper respiratory tract infection, urinary tract infection, viral infection
Musculoskeletal System: arthritis, joint pain, muscle or bone pain, leg cramps, muscle cramps

Nervous/Psychiatric System: anxiety, confusion, decreased concentration, depression, dizziness*, drowsiness*, irritability, mood swings, personality disorder, sleep disorder, worry
Respiratory System: coughing, fluid in sinus cavities, nasal congestion, sore throat, fluid in the lungs
Reproductive System: breast pain, breast tenderness, vaginal discharge, vaginal dryness, uterine fibroid
Skin: acne, night sweats
Eyes: blurred vision
Kidney and Urinary System: urinary problems
* Use caution when driving a motor vehicle or operating machinery as dizziness or drowsiness may occur.
During the marketing of PROMETRIUM Capsules, other adverse events have been reported, including reversible cases of liver problems, particularly in patients taking high doses. Additionally, rare occurrences of fainting and/or low blood pressure have also been reported.

These are some of the warning signs of serious side effects:

Be alert for unusual signs and symptoms. If any of these warning signals (or any other unusual symptoms) happen while you are using PROMETRIUM Capsules, call your healthcare provider immediately:

- Breast lumps (Ask your healthcare provider to show you how to examine your breasts monthly.)
- Pain, swelling, or tenderness in the abdomen
- Tremors or seizures, migraine headaches, shortness of breath or asthma, heart problems, or kidney problems
- Abnormal bleeding from the vagina
- Feelings of depression
- Pains in the calves or chest; a sudden shortness of breath; or coughing blood, indicating possible clots in the legs, heart or lungs
- Severe headache, vomiting, dizziness, faintness, or changes in vision or speech; weakness or numbness in an arm or leg, indicating possible clots in the brain or eye

General information about safe and effective use of PROMETRIUM Capsules

- Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not take PROMETRIUM Capsules for conditions for which it was not prescribed.
- Your healthcare provider has prescribed this drug for you and you alone. Do not give PROMETRIUM Capsules to other people, even if they have the same symptoms you have. It may harm them.
- PROMETRIUM Capsules should be taken as a single daily dose at bedtime. Some women may experience extreme dizziness and/or drowsiness during initial therapy. In a small percentage of women, these effects may be increased including blurred vision, difficulty speaking, difficulty walking, and feeling abnormal. If you experience these symptoms, discuss them with your healthcare provider immediately. A single bedtime dose may reduce the impact of these symptoms.
- Use caution when driving a motor vehicle or operating machinery as dizziness or drowsiness may occur.

Keep PROMETRIUM Capsules out of the reach of children.

This leaflet provides a summary of the most important information about PROMETRIUM Capsules. If you would like more information, talk with your healthcare provider or pharmacist. You can ask for information about PROMETRIUM Capsules that is written for health professionals. You can get more information by calling the toll free number 1-800-241-1643.

What are the ingredients in PROMETRIUM Capsules?

Active ingredient: 100 mg or 200 mg micronized progesterone
The inactive ingredients for PROMETRIUM Capsules 100 mg include: peanut oil NF, gelatin NF, glycerin USP, lecithin NF, titanium dioxide USP, D&C Yellow No. 10, and FD&C Red No. 40.
The inactive ingredients for PROMETRIUM Capsules 200 mg include: peanut oil NF, gelatin NF, glycerin USP, lecithin NF, titanium dioxide USP, D&C Yellow No. 10, and FD&C Yellow No. 6.

HOW SUPPLIED

PROMETRIUM Capsules 100 mg are round, peach-colored capsules branded with black imprint “SV.”
PROMETRIUM Capsules 200 mg are oval, pale yellow-colored capsules branded with black imprint “SV2.”
Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].
Protect from excessive moisture.
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Catalent Pharma Solutions
St. Petersburg, FL 33716

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